REMARKS

Upon entry of the amendments set forth above, claims 1-20, 22-23, 25-29 and 32-44 will be pending. New claims 39-44 are introduced above. Support for the language of claims 39-41 can be found, for example, in the Summary of the Invention, the latter half of page 7 of the specification, original claims 19 and 21, and examples 4, 5, 7 and 10. Support for new claims 42-44 can be found at the same pages of the specification and in original claims 19 and 24.

The present invention is directed to viral vector complexes in which a viral vector comprising a molecule or agent of interest is directly and non-covalently bound to a ligand capable of effecting or enhancing the binding or tropism of the viral vector to a desired target cell, such as a cancer cell. The admixture can be administered *in vivo* to a human or other animal to accomplish targeted delivery of the contents of the viral particle, such that the molecule of interest is delivered to the target cell with specificity and high efficiency. The molecule of interest can sensitize the target cell to radiation and/or chemotherapeutic agents.

In the parent case, all of the then pending claims were rejected under 35 U.S.C. §112, first paragraph, on the basis that

the specification was not enabling for the full scope of the subject matter of the claims. More specifically, the examiner asserted that the application does not enable methods for providing the viral vector complexes of the invention to an animal for treating head and neck, bladder, breast, thyroid, ovarian or prostate cancer, melanoma or lymphoma. He also asserted that the application does not enable a method for treating brain tumors, which he asserted fall within the scope of the cancer types listed above. He further asserted that a ligand-mediated cell targeting can succeed only when the ligand is used for delivering a gene of interest to a tumor type over-expressing the ligand receptor and that although the expression of some ligand receptors on different cancer cells was known in the art, the specification fails to provide sufficient enabling disclosure for the full scope of the invention claimed. The specification was said to fail to provide adequate guidance and evidence regarding the delivery of the claimed vector comprising any of a variety of different cell-targeting ligands and therapeutic agents such that the delivery would result in a therapeutic effect in the recipient. This rejection is traversed.

As an initial point, Applicants wish to address the examiner's continued concern that head and neck cancer includes

brain cancer. Attached to this Amendment are pages from the National Cancer Institute website. These pages describe and define head and neck cancer and make clear that the term does not include brain cancer. Nor does it include cancers of the eye, thyroid, scalp, skin, muscles or bones of the head. Rather, head and neck cancer refers to cancers which begin in the oral cavity, salivary glands, paranasal sinuses and nasal cavity, pharynx, larynx, or lymph nodes in the upper part of the neck. this is made clear in both the NCI's general discussion of head and neck cancer and in its dictionary definition of the term (pages from both part of the website are provided). Another website, the head and neck cancer website (www.hncancer.com) notes that head and neck cancer commonly is referred to as throat cancer (page enclosed). Applicants respectfully submit that in view of this evidence it should be clear that the cancer types listed in Applicants' claims do not include brain cancer.

Applicants also note that the examiner's comment that the "target cell" in claim 1 encompasses brain cancer cells is irrelevant. Claim 1 and dependent claims 2-16 and 33-37 are composition claims directed to a combination of a virus and a ligand. These claims are enabled if the application teaches how to make and use the vectors which, as discussed below, Applicants have done. The target cell is not part of the composition being

claimed, and so theorizing as to the scope of possible target cells or uses is not relevant to determining the patentability of the vectors themselves.

Applicants believe that it is helpful to address the claims to the composition and the method of making the composition (claims 1-18 and 33-36) and the claims to methods of using the compositions (claims 19-20, 22-23, 25-29, 32 and 38-44) separately, and the discussion below is so arranged.

The vectors and method of making them

As Applicants have explained in detail during prosecution of the parent application, they have provided a number of examples describing the preparation of vectors in which a ligand is bound directly to a ligand. They have illustrated this using three different types of targeting ligands (transferrin, a single chain antibody fragment (TfRscFv) and a protein (epidermal growth factor (EGF)) and three different types of viruses (adenovirus, a retrovirus and herpes simplex virus) comprising either of two different nucleic acids of interest (one encoding p53 and one encoding Lac Z). The three viruses chosen represent three very different types of viruses which have different sizes and mechanisms of action and illustrate well the scope of the invention.

Similarly, the ligands exemplified in the examples illustrate that a variety of ligands can be used in the intention. Useful ligands are proteins, peptides, hormones, antibodies and antibody fragments which specifically target the viral vector to cells which contain receptors for the ligand or which can internalize the ligand by receptor-mediated endocytosis. Selection of a suitable ligand is a matter of routine experimentation based on the nature and characteristics of the target cells of interest. As Applicants previously have noted, much research has been done in recent years to characterize different cancer types and to identify receptors associated with various cancer types. In the last Office Action in the parent application, the examiner stated that although the expression of some ligand receptors on different cancer cells was known in the art, the specification fails to provide sufficient enabling disclosure for the full scope of the intention claimed. This is a conclusory statement on the examiner's part and cannot suffice as a basis for upholding the rejection of claims 1-18 and 33-36. Applicants have given several specific examples of ligands which are over-expressed on a variety of types of cancer cells. If one wished to focus on a cancer that is less fully characterized in the scientific literature, only routine experimentation is required to determine useful ligands for

targeting a vector to the particular type of cancer cell. Western blot analyses, for example, which are a very standard and routine type of test, can be carried out to determine if receptors to a ligand of interest are over-expressed on the cell.

Applicants do not need to provide a specific example for each and every type of cancer cell. It is well-settled case law that paragraph 1 of §112 of the patent statute does not require a specific example of everything within the scope of a broad claim. *In re Anderson* 176 USPQ 331, 333 (CCPA 1973). The enablement provision of the patent statute requires that an Applicant provide persons of skill in the art with a specific and useful teaching. This the current Applicants have done. they have described useful viruses, nucleic acids of interest and useful ligands. they have taught a very simple and straightforward method of preparing the viral vectors, and they have shown in the Examples of their application that the viral vectors do target cells of interest efficiently such that high levels of the nucleic acid carried by the virus can be expressed in the target cell. This is all that is required for enablement of the claims to the vectors and the methods of making them.

Administration of the viral vectors

Claim 19 has been amended to be clearly directed to a method for targeting delivery of a nucleic acid to a cancer cell. By their invention, Applicants have found a way to enhance the binding or tropism of a viral vector comprising a nucleic acid or other molecule of interest to selected target cells. Viral vectors are used in the majority of gene therapy protocols in clinical trials. As Applicants have indicated in their specification, although viral vectors offer a number of advantages for use in gene therapy, to date they have not been as successful as desired because upon administration the particles do not sufficiently target the cells of interest such that effective amounts of the nucleic acid or other agent of interest ultimately are expressed in those target cells. Efforts to improve the tropism or binding of viruses by conjugating them to ligands often have involved harsh or complicated processing steps, which inadvertently can cause inactivation of some of the viral particles and, therefore, decreased infectivity of the target cells. Applicants' invention addresses both of these recurring problems. Applicants have found that viral particles can be simply admixed with a single ligand such that the ligand non-covalently binds directly to the virus. The ligand can be selected on the basis that a receptor for the ligand is over-

expressed on the target cell of interest, such that upon administration, the ligand also will bind directly to the receptor on the target cell. The viral vector complex of the present invention thus is a simple, two-component system that enhances viral-mediated gene delivery to target cells.

The Examples in the application show that viral vectors of the present invention do efficiently deliver the nucleic acid of interest to the target cancer cells. Depending upon the particular nucleic acid selected, expression of the nucleic acid can result directly in a therapeutic, anti-cancer effect, and/or it can sensitize the cells to radiation or chemotherapy agents such that when such agents subsequently are administered they are much more effective than when administered independently. In the last Office Action of the parent application, the examiner stated that it appeared that delivery of a vector comprising p53 nucleic acid alone failed to provide therapeutic effect *in vivo*. Applicants respectfully direct the examiner's attention to Figures 5A-5H of the application. These images show images of mouse lungs with melanoma metastases following an experiment in which mice received no treatment (Figures 5A and 5E), the chemotherapeutic cisplatin alone (Figure 5B), untargeted adenovirus-p53 and cisplatin (Figure 5C), a targeted complex of transferrin-adenovirus-LacZ (Figure 5F), transferrin-targeted

adenovirus-p53 (Figure 5G) or a combination of transferrin-targeted adenovirus-p53 and cisplatin (Figure 5D and 5H). Low doses of the viral vectors were administered. Figure 5G shows tumor reduction as a result of the administration of the transferrin-targeted Ad-p53 alone. Attached to this amendment is a color copy of Figures 5A-H, which shows more clearly than the black and white copy of the Figures that the lung of Figure 5G shows significantly fewer tumor colonies than the untreated lungs, the lung treated with cisplatin alone, the lung treated with untargeted viral vector and cisplatin or the lung treated with cisplatin and targeted vector containing LacZ. Although the combination therapy of targeted viral vector plus chemotherapy in this instance shows more dramatic results, with no obvious tumor metastases remaining, administration of the targeted tumor alone, even at a low dose of administration, did result in noticeable lung improvement.

New independent claims 39 and 42 are directed to a method of specifically targeting and sensitizing cancer cells to radiation or chemotherapy. Several examples in the application specifically illustrate this aspect of the invention. The examiner has criticized the experiments described in these examples as involving the administration of the vectors to mice with human tumor xenografts rather than the administration to

humans with cancer. The examiner has failed to provide any objective evidence to indicate that the results of the experiments of the Examples cannot be extrapolated to human cancer patients, however, and Applicants respectfully submit that in the absence of such evidence such a criticism cannot properly form the basis for sustaining the rejection. Applicants further note that dependent claims specifically identify the nucleic acid of interest as that encoding p53 and the identify the ligand as transferrin, the nucleic acid and ligand illustrated in the Examples of the application.

New claims 40 and 43 are directed to a method of increasing the levels of expression of a nucleic acid of interest in target cancer cells. Increased levels of expression when the targeted viral vector is administered *in vivo* are shown in the Western blot analyses presented in Figure 3 of the application. As explained in Example 3, the Western blot analysis of tumors from mice receiving targeted Ad-p53 revealed an upper band, representing exogenous p53, and a lower band, representing endogenous DU145 p53, that merged into what appears in the figure as one large band. This clearly shows that there is significantly more exogenous p53 in tumors from mice receiving the targeted transferrin-Adenovirus-p53 than the tumors from the mice receiving the untargeted Ad-p53. Importantly, as explained

in the Example, liver and other vital organs from the mouse treated with the targeted viral vector showed little or no exogenous wtp53 (thus showing that the vector did target the tumor), whereas treatment with the untargeted vector resulted in a higher level of exogenous p53 in the liver. As expected, tumors of the mice who were untreated contained only the endogenous DU145 p53 and organs of these animals contained only endogenous mouse p53. These results clearly illustrate that the Tf-Ad-p53, and not untargeted Ad-p53, selectively targets tumors *in vivo* and that p53 is expressed efficiently in tumor tissue. This targeting and expression, of course, is not limited to delivery of p53. This is illustrated by Figures 2A-2F and the accompanying discussion in the application. As discussed in Example 2, these figures show that the injection of transferrin-Ad5LacZ resulted in tumors with increased X-Gal-stained blue cells, as compared with Ad5LacZ alone, and that no β-galactosidase expression was evident in the liver or other organs, including spleen and lung. A color copy of Figures 2A-2F also is provided with this Amendment. As discussed in Example 2, quantitative β-galactosidase assays also confirmed the substantial increase of gene expression in tumors of mice injected with transferrin-targeted adenovirus, compared with that of the virus alone. These results show that the targeted-viral

vector of the present invention can be administered to deliver a variety of genes of interest to target cells and that the targeting is shown by high levels of expression of that gene.

Finally, new claims 41 and 44 are directed to an improvement in a method of administering a chemotherapeutic or radiation therapy agent by first administering a viral vector complex of the invention to sensitize the cancer cells to the chemotherapy or radiation therapy. Again, these claims are clearly illustrated in, and embodied by, the Examples of the application, such as Examples 5 and 7.

Applicants thus respectfully submit that all of the pending claims meet the requirements of §112, paragraph 1, of the patent statute.

Rejections based on prior art

Claims 1-4, 6, 8-11, 17 and 18 remain rejected, and claim 34 is rejected, under 35 U.S.C. §102(b) as being anticipated by Douglas et al., *Intl. J. Oncology* 11:341-348 (1997). The examiner dismissed Applicants' previous arguments that the reference does not teach directly binding a ligand to a virus but rather requires binding the ligand through a neutralizing Fab fragment of a monoclonal antibody, saying that the neutralizing Fab fragment of an anti-knob antibody also is considered a ligand

and the Fab fragment is complexed to the adenovirus. This rejection is traversed.

Douglas et al. teach a three component vector system for delivering a virus to a target cell. Specifically, the Douglas et al. vector system requires (1) an adenovirus, (2) a neutralizing anti-knob antibody capable of blocking the primary interaction between the adenovirus and its cognate cellular receptor and (3) a ligand which recognizes a specific cell surface receptor chemically conjugated to the antibody. This vector system is clearly illustrated in Figure 2 of the Douglas et al. paper (page 344).

In contrast to this three component vector system, the vector claimed in the present application is a two component system. The vector of the present invention consists essentially of a cell-targeting ligand and a virus to which the ligand is directly bound non-covalently. The examiner asserted that the two systems were the same, averring that the neutralizing Fab fragment of an anti-knob antibody also is considered a ligand which was complexed to the virus. The antibody is complexed to the adenovirus, but it is not also complexed directly to the target cell. All of the independent claims of the present application specify that the ligand binds directly to both the virus and the target cell. The written description and Figure

2, as noted above, are clear that the vector system described and recommended by Douglas and his colleagues requires three components. If one wishes to label the antibody as the ligand, as the examiner has done, the Douglas et al. vector is distinguishable from that claimed by Applicants in that there is a linker between the ligand and the target cell that is not found in the Applicants' vector. If one considers folate as the ligand, the Douglas et al. vector is distinguishable from that claimed by Applicants in that there is a linker between the ligand and the virus that is not found in the Applicants' vector. The vector of claim 1 of the present application and the claims dependent upon it thus represent an advance over prior art vectors, such as that taught by Douglas et al., and is distinguishable over such vectors.

The other independent claim rejected as anticipated by this reference, claim 17, directed to a method of making a vector, also specifically requires that the ligand bind directly to both the virus and the target cell. This claim thus also is novel over the teachings of Douglas et al.

Claims 1-4, 6, 8-10, 12, 17 and 18 remain rejected under 35 U.S.C. §102(e) as anticipated by U.S. Patent 5,994,109, issued to Wu et al. The examiner asserted that the system taught in the '109 patent has a binding molecule that can noncovalently link to

a nucleic acid, such as a virus, and covalently link to a surface ligand. The examiner asserted that the binding molecule can be considered a ligand which binds directly to viruses and to another ligand for cell-specific delivery of a nucleic acid. This rejection is traversed.

As discussed above, independent claims 1 and 17 each require that the ligand bind directly to both the virus and to the target cell. The vector systems of the present invention thus are simple and elegant two-part systems. In contrast to this, the systems disclosed in the '109 patent, as the examiner recognized, are all three molecule systems, comprising a ligand, a binding molecule, which the examiner considers to be a second ligand, and DNA, such as a virus. The same argument set forth above in the discussion of the Douglas et al. reference is equally applicable here. As the reference does not teach or suggest a vector system in which a single ligand binds directly to both a virus and a

target cell, the reference does not anticipate the claims of the present application.

Respectfully submitted,

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